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AUTHOR(S):

KOMAKI, KATSUHIKO

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# Comparative Study on Vagotomy Procedures in Relation to Biliary Composition

KATSUHIKO KOMAKI

Department of Surgery, Osaka Kita Teishin Hospital

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## Introduction

Since 1964 HIKASA et al[1]. have studied the pathogenesis of cholesterol gall stones in animals and humans. They concluded that changes in dietary composition, such as fat, carbohydrate and indigestible fibers, influence the formation of cholesterol gall stones. SHIODA[2] found differences in biliary out-put between day and night as well as fed and fasted cholecystectomy patients maintained on well-defined dietary regimens, and suggested that some factors other than diet, such as hormones or autonomic nerves, might affect bile formation. DRAGSTEDT[3] found that vagotomy was effective in the treatment of peptic ulcers. Since then many clinical investigators have reported their results to support the value of vagotomy, while others have reported untoward side effects of vagotomy, such as fat malabsorption, biliary dysfunction and cholelithiasis[4], suggesting that transection of the trunks of the vagus nerves have a definite influence on the biliary system. Present experimental studies were, therefore, designed to investigate the effect of vagotomy on bile formation in dogs.

## Materials And Methods

*Animals*

Adult male mongrel dogs weighing 10 to 15 kg were divided into two groups; one for truncal vagotomy and the other for selective gastric vagotomy. They were maintained on a chow diet throughout the experiments.

*Solvents*

Solvents were of reagent grade. They were re-distilled before use, with the exception of n-butanol and acetic acid.

*Procedures of Truncal Vagotomy*

All the animals were fasted for 24 hours before surgery. They were anesthetized with IV Nembutal. A tracheal tube was inserted and connected to a Harvard respirator with a frequency adjusted to 10 to 15 per minute and a volume of 200 ml per breath. Muscle relaxants were not used because of delay in awakening. The thorax was entered via a left anterior incision which was made in the sixth or seventh intercostal space. The lower

Key words : Vagotomy; truncal vagotomy, selective gastric vagotomy.

Present address : Department of Surgery, Osaka Teishin Hospital. 35, Yamazaki-cho, Kita-ku, Osaka, Japan. 〒 530

esophagus was reached easily by retracting the heart anteriorly and the left lung superiorly. The left and right trunk and communicating branches of the vagus nerves were all transected by ligation above the diaphragm. The thorax was closed in layers, leaving a Nelaton's drain tube which was removed after suction under negative pressure for three hours. No IV fluids were given during or after surgery. They received ordinary food and IM chloramphenicol, 1 g per day, for three days after surgery. Pyloroplasty was not performed in any of the animals. This group was designated the TV-group.

*Procedures of Selective Gastric Vagotomy*

The animals were anesthetized by Nembutal. The abdominal cavity was entered via an upper middle incision. The gall bladder was punctured to obtain bile for chemical analysis (controls). The vagus nerves ramify radically beneath the diaphragma in dogs, so the branches entering the stomach were transcted by multiple ligations along the lesser and greater curvature from the cardia to the pyloric ring. In this manipulation many gastric arteries and veins were transected along with the gastric vagal branches, except for the right gastric, right gastroepiploic and short gastric arteries and veins. Pyloroplasty was not performed. The animals which received selective gastric vagotomy were designated the SV-group.

*Method of Obtaining Bile Specimens*

Two to 10 ml of bile was obtained by needle puncture of the gall bladder through a small rectus or pararectus incision after general anesthesia with IV Isozol, 200 to 300 mg. The needle hole in the punctured gall bladder was closed by ligation with fine catgut, followed by layered closure of the wound. The bile specimen thus obtained was stored in a refrigerator before use. Bile samples were obtained from both groups 4, 6, 8, 12, 16, and 24 weeks after vagotomy.

## Analysis of Bile

*Extraction of Bile Acids, Phospholipids, And Cholesterol*[5]

An aliquot of bile (2 ml) was mixed with 20 times its volume of Folch's solution (chloroform : methanol = 2 : 1)[6]. The solution was filtered through glass wool to eliminate small protein residues in a graduated cylinder with a glass stopper. Distilled water equal to 20% of the volume of the solution was added, the mixture was mixed by inverting, and allowed to separate into two clear layers. The top layer was removed completely by pipetting, and additional distilled water equal to 20% of the volume of the lower layer was added to the lower layer, and the mixture was mixed again. After separation, the second top layer was removed and combined with the first top layer. The combined top layers were evaporated to dryness under reduced pressure in a rotary evaporator at 60°C. The residue was redissolved in solvent mixture (methanol : water = 85 : 15) and made up to 10 ml in a 10 ml graduated tube with a stopper. This was designated "top layer stock solution". The bottom layer was evaporated under nitrogen, redissolved in solvent mixture (cholesterol : methanol = 9 : 1), and made up to 10 ml in a 10 ml graduated tube.

This was designated "bottom layer stock solution". Both stock solutions were stored at 4°C till use.

*Determination of Bile Acids*[5]

From the top layer stock solution 4 ml (corresponding to 0.8 ml of the original bile) was transferred to a 200 ml Teflon bottle with a Teflon screw cap, methanol was evaporated under nitrogen stream, and 10 ml of 1 N aqueous NaOH was added. The bottle was tightly capped and heated in an autoclave at 15 psi for three hours. The mixture was then acidified to pH 1 with 3 N HCl, transferred to a glass separating funnel, and extracted six times with 30 ml of diethyl ether. The combined extracts were washed twice with 20 ml of distilled water and the solution was evaporated to dryness. The mixture of deconjugated bile acids thus obtained was dissolved in a few drops of methanol in a 20 ml container with a screw cap. Excess amounts of the freshly prepared ethereal diazomethane with p-toluenesulfonyl-N-methyl-N-nitrosoamide, and KOH were added to the deconjugated bile acids. After being kept in a dark room for 15 minutes, the volatile components were removed under nitrogen. The procedure was repeated again to ensure complete conversion of the free bile acids to methyl esters.

Thin-layer chromatographic separation of bile acids was carried out with 0.5 mm layers of Silica Gel G (E. Merck AG, Darmstadt, Germany) on 20×26 cm plates. The plates were washed to remove absorbent contaminants from the working area by allowing a solvent mixture of chloroform-methanol-water 85 : 35 : 5 (v/v) to rise to the top of the plates. The TLC plates were then dried and activated at 120°C for 1 hour. The mixture of methyl esters of bile acids was applied as a streak to a TLC plate. The plate was developed in a solvent mixture of petroleum ether-isopropyl ether-acetic acid 2 : 1 : 1, dried for 1 hour in a draft chamber, and sprayed with 0.01% (w/v) Rhodamine 6G in ethanol solution. The three bands of methyl ester of deoxycholic, chenodeoxycholic and cholic acid (from top to bottom) were marked under an UV lamp, scraped with absorbent by a razor blade, and eluted with 50 ml of diethyl ether. In this procedure care should be taken to keep the developed plate under an air current till there is no smell of acetic acid. The methyl esters were weighed and dissolved in 10 ml of methanol.

Appropriate aliquots of the solutions containing unknown amounts (less than 80 $\mu$g) of methyl esters of cholic, chenodeoxycholic, and deoxycholic acid were transferred to 10 ml tubes, and the solvent was evaporated. A solution of 4 ml of freshly prepared 65% sulfuric acid was added and mixed thoroughly, and the tubes were heated at 60°C ± 1°C for 1 hour. The tubes were then transferred to a cold water bath for a few minutes to stop further production of UV-absorbing substances. Measurement of UV absorption of individual bile acids was performed on a Beckman DU spectrophotometer; cholic acid methyl ester was measured at 320 m$\mu$, chenodeoxycholic acid at 380 m$\mu$, and deoxycholic acid at 385 m$\mu$ aginst a blank of 4 ml of 65% sulfuric acid, which was treated in the same way as the unknown samples. Known amounts of methyl esters of three bile acids which were purified by thin-layer chromatography before use were also treated in the same way at the same time.

*Determination of Cholesterol*[7)8)]

Cholesterol is excreted into the bile in its free form in dogs as in humans. It is important to eliminate bile pigment, bilirubin, from bile samples as completely as possible for colorimetric determination of cholesterol. Cholesterol in the bottom layer stock solution was, therefore, purified by digitonization.

From the bottom layer stock solution 0.5 ml (corresponding to 0.1 ml of original bile) was added to 1 ml of 1% digitonin-ethanol solution, allowed to stand at room temperature for 30 min, and centrifuged at 3,500 rpm for 5 min. After complete removal of the supernatant, the residue was added to 4 ml of acetone, mixed thoroughly, and spun down at 3,500 rpm for 5 min to eliminate other contaminants than cholesterol digitonide. After discarding of the supernatant, the residue was dissolved in 3 ml of glacial acetic acid, added to 2 ml of a freshly prepared color reagent mixture consisting of ferric chloride, concentrated phosphoric and sulfuric acid, shaken thoroughly, and read on a colorimeter at 560 mμ against a blank with 0.5 ml of distilled water which was treated in the same way as the unknown samples. All determinations were made in duplicate and finished within 30 min.

*Determination of Phospholipids*[9)]

A modification of Höflmayer-Fried's method was used for the determination of inorganic phosphorus in the phospholipids extracted from bile.

From the bottom layer stock solution 0.2 ml (corresponding to 0.04 ml of original bile) was evaporated to dryness under nitrogen. The residue was added to 0.5 ml of 70% perchloric acid solution and 0.1 ml of 65% nitric acid, digested at 190°C in an oil bath for 20 min, and cooled in a water current. The digested solutions were added to 0.5 ml of 7% ammonium molybdate solution and 0.5 ml of a reducing reagent mixture consisting of hydroquinone, sodium bisulphite and distilled water, mixed well, and allowed to stand at room temperature for 20 min. Measurement of the colored tubes was performed at 660 mμ on a spectrometer within 30 min. All determinations were carried out in duplicate. A blank of 0.2 ml of distilled water and standard samples containing known amounts of phosphorus were treated in the same way at the same time.

## Results

*Macroscopic Changes*

All the animals in the TV-group showed remarkable hypotonic dilatation of the stomach and the gall bladder in the fourth postoperative week, while those in the SV-group did not show any change in size of the gall bladder but did have stomach dilatation. The stomach did not, however, contain food residue after 24 hour fasting in animals of either group. The gall bladders did not show any inflammatory change except for tiny scar formation at the site of puncture, despite repeated paracentesis. All the animals in the TV-group had, in general, darker and more viscous bile than preoperative bile specimens. Amorphous pigment stones as shown in Fig. 1 or sand was found in two thirds of them. These

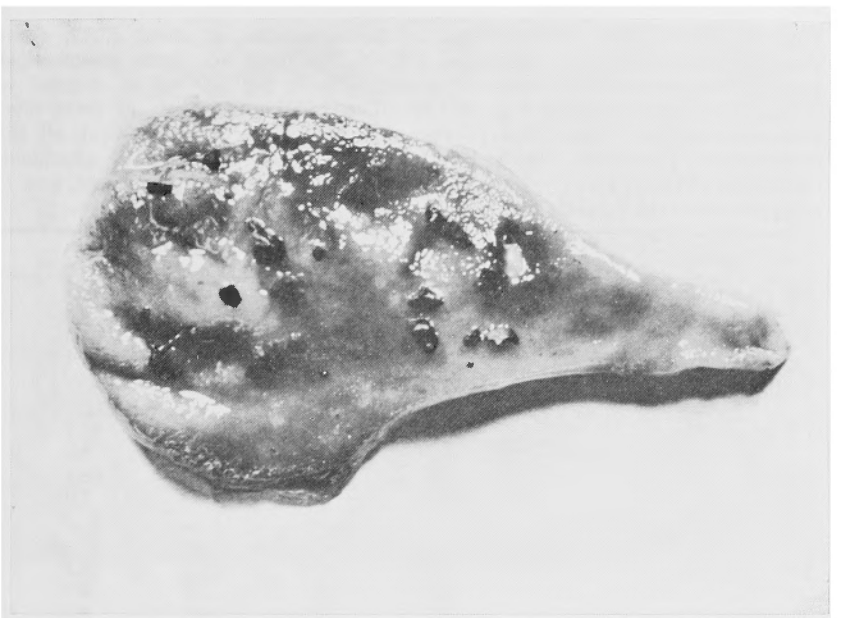

**Fig. 1** Several amorphous pigment stones were found in the gall bladder of a dog which was sacrificed after the twenty-fourth postvagotomy week.

macroscopic changes were observed frequently in the TV-group throughout the present study, whereas cholesterol gall stones were not found. No other abnormal macroscopic changes were found in the common duct, liver, or small and large intestines in most of the animals in the two groups.

*Changes of Bile Components*

In the present study the concentration of bile acids, phospholipids, and cholesterol in each bile sample was determined initially in mg per ml of bile and translated to millimoles per liter of bile. The relative quantity of total bile acids, cholic, chenodeoxycholic, and deoxycholic acid, phospholipids, and cholesterol was expressed as percentages of all these five components. The ratios of total bile acids to cholesterol, phospholipids to cholesterol, and trihydroxy-cholanoic acid to dihydroxycholanoic acid were calculated in order to determine the effect of vagotomy on the major biliary components in relation to the lithogenecity of bile. Individual data are summarized in Table 1.

Total bile acids, expressed as the sum of cholic, chenodeoxycholic and deoxycholic acids, tended to decrease postoperatively in the TV-group, while in the SV-group they returned to normal after a small rise and fall as shown in Figs. 2 and 3. Cholic acid showed a significantly lower level from the fourth to the twenty-fourth postoperative week in the TV-group as compared with the SV-group and the controls. Cholic acid in the SV-group showed lower values at the fourth, sixth, and twelfth week than in the controls, but it increased and returned to the same level as in the controls after the sixteenth week, while the mean values of cholic acid at each postoperative week stayed above those of the TV-

**Table 1.** Total bile acids (TBA) are expressed as the summation of cholic (CA), chenodeoxycholic (CDCA), and deoxycholic acid (DCA). The three bile acids, phospholipids (PL), and free cholesterol (FC) are all determined in mg per ml of original bile and translated to millimoles per liter of bile. The relative quantity of total bile acidss, phospholipids, and cholesterol are expressed finally as percentages of all the three components. The ratios of total bile acids to cholesterol (TBA/C), phospholipids to cholesterol (PL/C), and trihydroxycholanoic acid to dihydroxycholanoic acid (Tri/Di) are also calculated in each bile sample.

| | | | 4 | 6 | 8 | 12 | 16 | 24 weeks |
|---|---|---|---|---|---|---|---|---|
| TBA | TV-group | Mean | 93.6 | 92.3 | 91.3 | 92.4 | 90.7 | 90.2 |
| | | ± SD | 0.5 | 0.7 | 3.0 | 1.6 | 2.1 | 2.9 |
| | SV-group | Mean | 89.3 | 91.9 | 94.4 | 91 9 | 94.0 | 94.0 |
| | | ± SD | | 4.2 | 2.8 | | 1.4 | 1.8 |
| | Controls | Mean | 94.7 | | | | | |
| | | ± SD | 1.4 | | | | | |
| CA | TV-group | Mean | 46.4 | 48.4 | 46.0 | 46.4 | 45.7 | 43.4 |
| | | ± SD | 14.5 | 10.5 | 3.9 | 13.9 | 9.6 | 8.2 |
| | SV-group | Mean | 55.9 | 49.9 | 66.5 | 54.8 | 68.1 | 63.1 |
| | | ± SD | | 12.1 | 9.3 | | 7.9 | 11.7 |
| | Controls | Mean | 63.3 | | | | | |
| | | ± SD | 11.8 | | | | | |
| CDCA | TV-group | Mean | 13.1 | 15.9 | 14.2 | 13.7 | 15.4 | 18.9 |
| | | ± SD | 4.0 | 4.5 | 4.4 | 3.6 | 3.6 | 5.6 |
| | SV-group | Mean | 15.3 | 12.5 | 8.5 | 9.1 | 8.0 | 7.4 |
| | | ± SD | | 8.7 | 1.3 | | 2.8 | 2.4 |
| | Controls | Mean | 9.5 | | | | | |
| | | ± SD | 5.4 | | | | | |
| DCA | TV-group | Mean | 34.1 | 28.0 | 31.0 | 32.3 | 29.6 | 27.9 |
| | | ± SD | 16.1 | 9.3 | 9.8 | 10.7 | 6.8 | 2.0 |
| | SV-group | Mean | 18.1 | 29.5 | 19.5 | 28.1 | 17.9 | 23.5 |
| | | ±S D | | 8.5 | 6.8 | | 7.3 | 8.2 |
| | Controls | Mean | 21.5 | | | | | |
| | | ± SD | 5.7 | | | | | |
| FC | TV-group | Mean | 0.34 | 0.36 | 0.43 | 0.40 | 0.45 | 0.63 |
| | | ± SD | 0.05 | 0.09 | 0.29 | 0.10 | 0.13 | 0.17 |
| | SV-group | Mean | 0.40 | 0.58 | 0.33 | 0.40 | 0.38 | 0.28 |
| | | ± SD | | 0.22 | 0.19 | | 0.13 | 0.05 |
| | Controls | Mean | 0.24 | | | | | |
| | | ± SD | 0.05 | | | | | |
| PL | TV-group | Mean | 9.4 | 8.9 | 9.4 | 9.1 | 8.4 | 8.9 |
| | | ± SD | 1.5 | 2.4 | 1.0 | 1.5 | 1.1 | 1.5 |
| | SV-group | Mean | 10.7 | 8.1 | 8.1 | 6.8 | 8.1 | 8.6 |
| | | ± SD | | 0.6 | 0.7 | | 1.0 | 1.0 |
| | Controls | Mean | 8.2 | | | | | |
| | | ± SD | 0.5 | | | | | |
| PL/C | TV-group | Mean | 18.7 | 20.8 | 21.8 | 17.8 | 21.2 | 14.7 |
| | | ± SD | 4.5 | 5.0 | 4.6 | 1.7 | 3.9 | 2.9 |
| | SV-group | Mean | 26.0 | 12.5 | 15.8 | 17.9 | 16.4 | 22.1 |
| | | ± SD | | 3.5 | 2.3 | | 5.6 | 2.1 |
| | Controls | Mean | 22.8 | | | | | |
| | | ± SD | 1.0 | | | | | |
| TBA/C | TV-group | Mean | 285.9 | 262.9 | 277.9 | 237.2 | 224.1 | 153.2 |
| | | ± SD | 56.0 | 64.0 | 153.6 | 52.3 | 65.9 | 61.1 |
| | SV-group | Mean | 226.5 | 172.3 | 325.2 | 229.0 | 289.1 | 380.7 |
| | | ± SD | | 56.5 | 124.2 | | 127.2 | 120.6 |
| | Controls | Mean | 429.7 | | | | | |
| | | ± SD | 144.7 | | | | | |
| Tri/Di | TV-group | Mean | 1.13 | 1.20 | 1.03 | 1.11 | 1.07 | 0.95 |
| | | ± SD | 0.62 | 0.49 | 0.19 | 0.56 | 0.42 | 0.28 |
| | SV-group | Mean | 1.67 | 1.26 | 2.58 | 1.48 | 2.88 | 2.33 |
| | | ± SD | | 0.52 | 1.07 | | 1.20 | 1.13 |
| | Controls | Mean | 2.31 | | | | | |
| | | ± SD | 1.00 | | | | | |

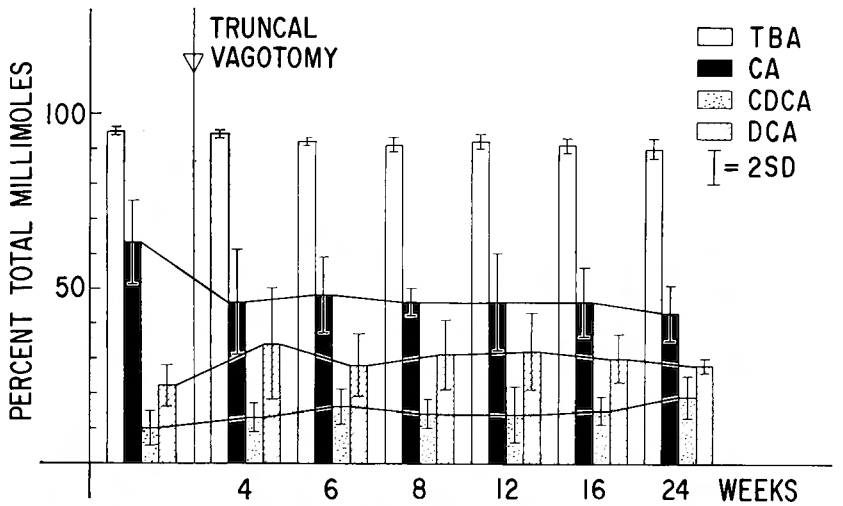


**Fig. 2.** Changes of total bile acids, cholic, chenodeoxycholic, and deoxycholic acid before and after truncal vagotomy.

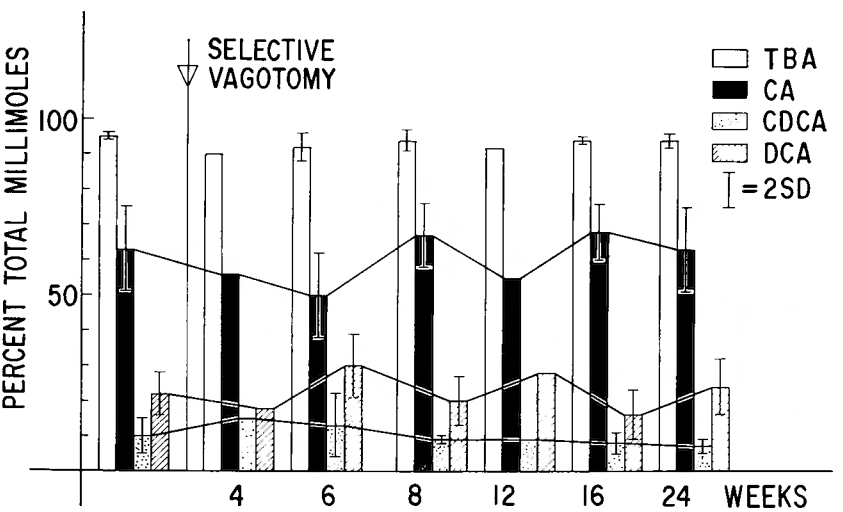


**Fig. 3.** Chages of total bile acids, cholic, chenodeoxycholic, and deoxycholic acid before and after selective gastric vagotomy.

group. Chenodeoxycholic acid in the TV-group maintained higher values than in the controls from the fourth to the twenty-fourth week, while that of the SV-group showed a gradual decrease to the normal level after the sixth week, as shown in Figs. 2 and 3. Deoxycholic acid in the TV-group showed a higher level than in the controls and SV-group throughout the whole course of the experiment except the sixth week, whereas in the SV-group it showed an increase at the sixth week but returned to normal after the eighth week. The most impressive of the postvagotomy changes in the three bile acids is that cholic acid in the TV-group decreased promptly after truncal vagotomy and maintained a

lower level than that of the SV-group and controls, while deoxycholic acid increased to a higher level as compensation for cholic acid, suggesting that truncal vagotomy had a definite influence on the metabolism of bile acids due to disturbance of the enterohepatic circulation, such as delayed intestinal motility, eccessive production of deoxycholic acid by prolonged exposure of cholic acid to the action of intestinal flora, inhibition of hepatic biosynthesis of the cholic acid by feed-back control, and so on.

Cholesterol was found in a free form in the bile of dogs. Cholesterol tended to increase postoperatively in the TV-group while it decreased gradually to normal in the SV-group, suggesting a possible effect of truncal vagotomy in producing unstable bile in which cholesterol gall stones might be initiated as shown in Fig. 4. Unfortunately, cholesterol gall stones were not seen in any of the animals of the TV-group because the concentration of cholesterol in dogs was much lower than in humans, less than 1/20 if the ratio of dog bile to that of human bile is cited as an example.

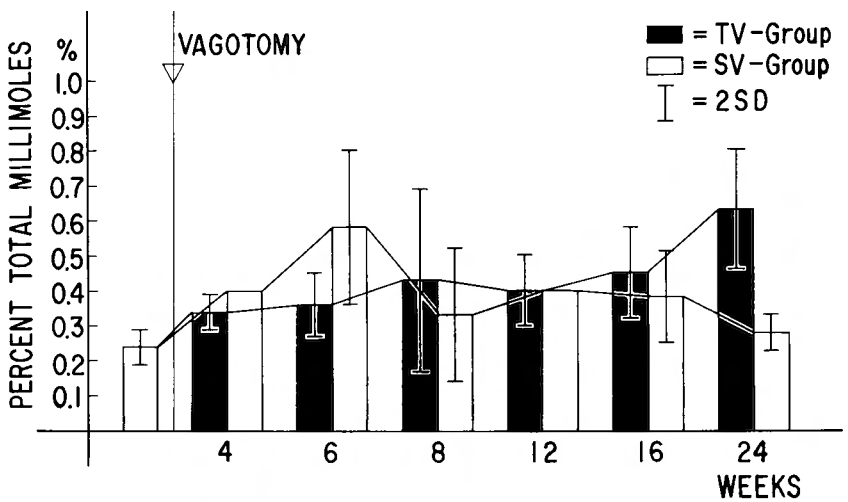


**Fig. 4** Changes of free cholesterol in TV- and SV-group.

Phospholipids did not show such a remarkable change as bile acids and cholesterol in relation to vagotomy in the present study, as shown in Fig. 5. However, the ratio of phospholipids to cholesterol (PL/C) showed an interesting tendency; it decreased to a significantly lower level in the TV-group at the twenty-fourth week than in the SV-group and controls, but it increased to normal in the SV-group, as shown in Fig. 6.

The ratio of total bile acids to cholesterol tended to decrease in the TV-group, as shown in Fig. 7, while that of the SV-group showed lower mean values than that of controls as well as the TV-group at the fourth, sixth, and twelfth week but increased after the sixteenth week and returned nearly to the normal range at the twenty-fourth week. The ratio of trihydroxycholanoic acid to dihydroxycholanoic acid was significantly lower than in the controls throughout the course of the experiment, while that of the SV-group showed

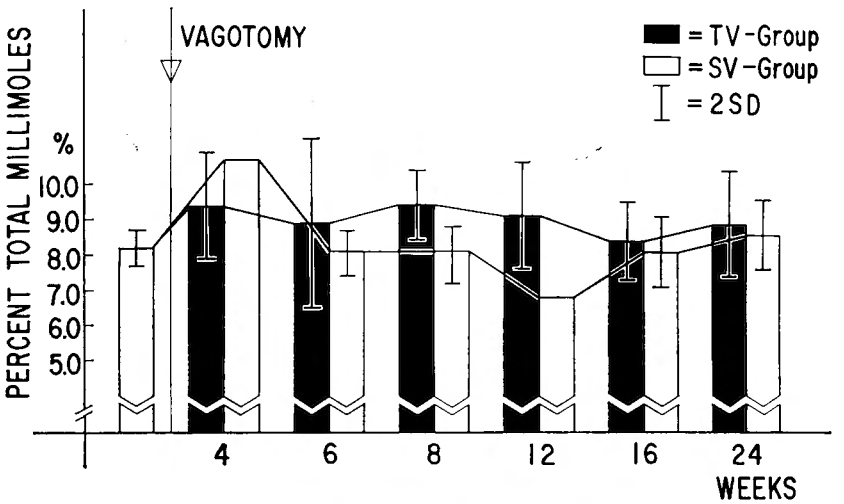


**Fig. 5** Changes of phospholipids in TV- and SV-group.

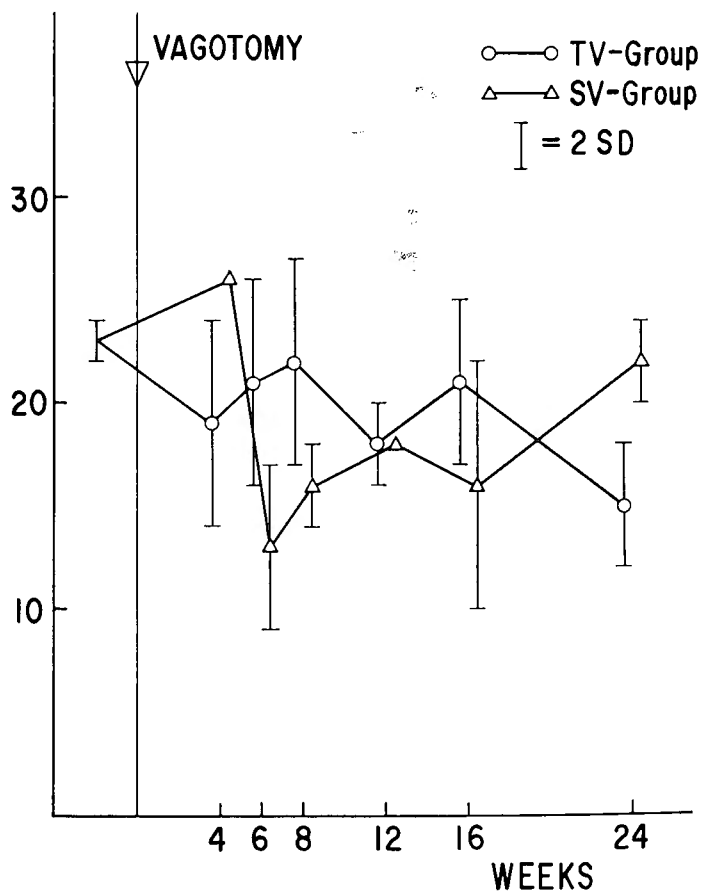


**Fig. 6** Changes of ratio of phospholipids to free cholesterol in TV- and SV-group.

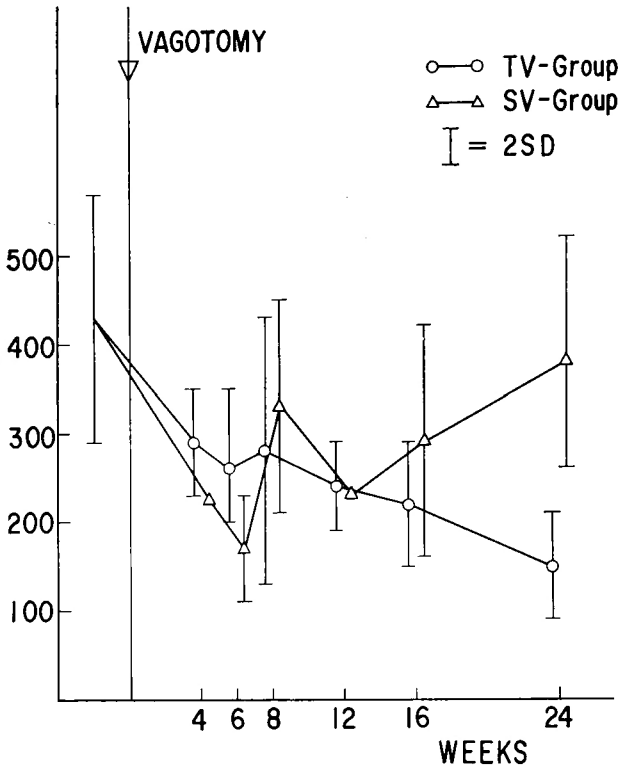


**Fig. 7** Changes of ratio of total bile acids to free cholesterol in TV- and SV-group.

the same level as in the controls at the twenty-fourth week after a slightly exaggerated undulatory change, as shown in Fig. 8.

The above-mentioned changes of the various parameters show that truncal vagotomy had a definite influence on the components of dog bile, which may facilitate formation of cholesterol gall stones by reducing the colesterol-holding power of bile. It is worthwhile to note that many of the animals receiving truncal vagotomy produced pigment stones or sand instead of cholesterol stones, suggesting a possible effect of truncal vagotomy on the physiological metabolism of bile pigments.

## Discussion

Since DRAGSTEDT first performed truncal vagotomy in the treatment of duodenal ulcer in 1943[3], clinical effectiveness of truncal vagotomy has been investigated by many surgeons. Recently, however, selective gastric vagotomy[10)-12)] or highly selective gastric vagotomy[13)-15)] has taken the place of truncal vagotomy because of untoward side effects of the latter. It is true that the vagus nerves are sacrificed usually in radical operations for malignant neoplasms of the esophagus and stomach. Some investigators insist on preservation of the

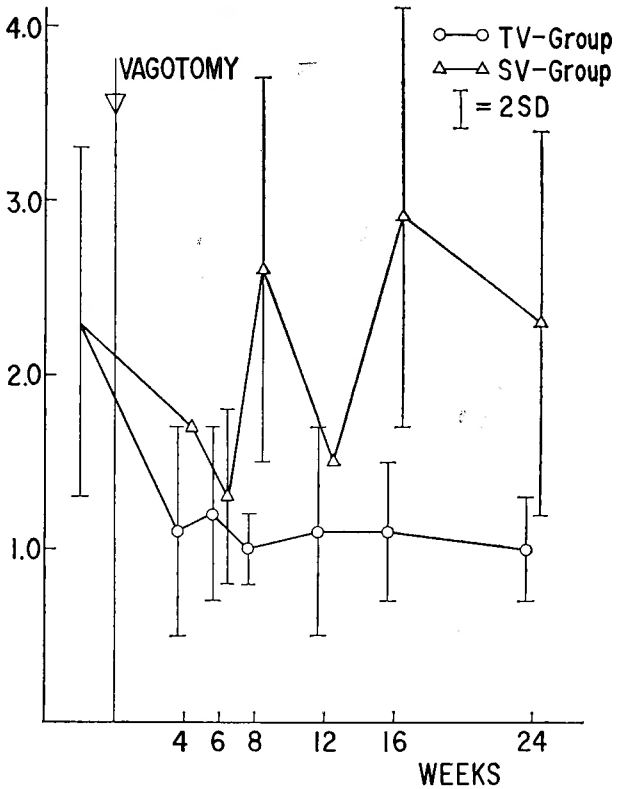


**Fig. 8** Changes of ratio of trihydroxycholanoic to dihydroxycholanoic acids in TV- and SV-group.

hepatic and posterior celiac branches of the vagus nerves in order to minimize postvagotomy side effects even in malignant cases[16] It is well known that diarrhea, fat malabsorption, delayed gastric emptying, and emaciation are caused by vagal denervation of the pancreas, liver, biliary and intestinal tracts. SHIODA et al. reported that fat absorption was remarkably inhibited in animals receiving truncal vagotomy as compared with those with selective gastric vagotomy and untreated controls[17]. ISHIGAMI et al. also reported that there was a difference in plasma concentration of triolein labeled with radioactive iodine between total gastrectomy patients in whom the vagal trunks were transected and those in whom the hepatic and posterior celiac branches were preserved selectively[16]; the former showed a significant decrease in fat absorption. Several clinical investigators reported that the transection of the posterior celiac[18] and/or hepatic branch[19][20] was responsible for the troublesome postvagotomy diarrhea. HENDRY et al. found in fact that diarrhea occurred in 23.3% of patients with truncal vagotomy but in only 9% of those with selective gastric vagotomy[21]. BASTABLE reported, however, in his study on the effect of vagotomy on the biliary system that the hepatic branch had no direct influence on postvagotomy diarrhea because there was no change in bilialy function after vagotomy[22]. It is said that the

stomach, duodenum, and gall bladder show vigorous movements when the main trunks of the vagus nerves are stimulated by an electric impulse while stomachs of which the gastric branches are all transected do not react to electric stimuli. The duodenum and the gall bladder show, however, good response when only the hepatic branch is preserved, while the duodenum, small intestines, and the right half of the colon show vigorous peristalsis when the posterior celiac branch is preserved but not the gastric and hepatic branches. In short, the physiological mobility of the digestive tract other than the stomach is well maintained if the hepatic and celiac branches are preserved in vagotomy[4]. We also found that the dogs in the TV-group showed hypotonic dilatation of the stomach and gall bladder while those in the SV-group had stomach dilatation only, giving not only good evidence of the observations which HARKINS et al.[4] described but also good confirmation of completeness in the surgical procedures of both truncal and selective gastric vagotomy.

In 1952, JOHNSON and BOYDEN reported that the gall bladder capacity of patients receiving truncal vagotomy increased to twice the preoperative capacity within a year, and concluded that some endocrine hormones appeared to be more prominent in controlling gall bladder contractions though they observed a decrease in the contracting speed of the gall bladder after vagotomy[23]. COX et al. found that the delayed contraction of the gall bladder which was often encountered after truncal vagotomy or partial gastrectomy might be due to a decreased secretion of cholecystokinin[24]. RUDICK and HUTCHINSON reported that hypotonic dilatation and impaired contraction of the gall bladder were eliminated by preserving the hepatic branch in their extensive study on gall bladder function in 53 patients who received truncal vagotomy[25][26]. INBERG and VUORIO[27], FAGERBERG[28], and PARKINS et al[29]. also reported that truncal vagotomy caused dilatation of the gall bladder but did not observe any dilatation of the gall bladder when the hepatic branch was preserved in selective gastric vagotomy or proximal selective gastric vagotomy. TINKER and COX did not comment on any hormonal influence on gall bladder contraction although they found that gall bladder contraction was suppressed by insulin-induced hypoglycemia in truncally-vagotomized patients as well as in those with selective gastric vagotomy[30]. WILLIAMS and GLANVILLE denied, however, the existence of postvagotomy dilatation of the gall bladder, insisting that there was no definite difference in the size of gall bladders between truncal and selective gastric vagotomy[31][32]. There are two opposing opinions in relation to the postvagotomy changes of the gall bladder. However, we should like to assume that the vagus nerves have a definite influence on the controlling mechanism of gall bladder contraction in animals and humans.

Other clinical investigators have reported a high incidence of cholelithiasis and cholecystitis in patients with truncal vagotomy[33]~[36] and gastric resection[37]~[40]. BARNETT and HILBUN found that human cholesterol gall stones were easily dissolved when they were transplanted into the gall bladder of a normal dog or of a dog after selective gastric vagotomy, though they were not dissolved so quickly in dogs after truncal vagotomy[41]. LOEB et al. challenged these observations, since they could not find similar changes in their

experimental study[42]. TOMPKINS et al. also found that delayed dissolution of transplanted human gall stones occurred in the gall bladder of dogs in which the vagus nerves were transected truncally, emphasizing a decrease in the ratio of phospholipids to cholesterol as a cause[43]. They also reported that the PL/C ratio might lead to precipitation of cholesterol and then to formation of cholesterol gall stones since the decreased PL/C ratio in dogs with truncal vagotomy was very colse to that of patients with cholesterol gall stones[44][45]. SHEEN et al. observed no change in the ratio of phospholipids to cholesterol after truncal vagotomy[46]. FLETCHER et al. found neither increase nor decrease in phospholipids or cholesterol[47], while COWIE reported a decrease in phospholipids after truncal vagotomy[48]. We found in the present study that the PL/C ratio in the TV-group showed a significant decrease in the twenty-fourth postvagotomy week as compared with that in the SV-group and untreated controls. We did not find such a low PL/C ratio as TOMPKINS et al. reported[43]. This discrepancy in the PL/C ratio may be due to differences between American and Japanese dog food.

Only a few investigators have reported changes in bile acid composition related to vagotomy; COWIE, WHITE and FLETCHER. COWIE and CLARK stated that the concentration of cholic acid showed a slight reduction after vagotomy, but this was not a statistically significant change[48]. FLETCHER and CLARK observed a reduced concntration of cholic acid[47]. WHITE et al. found a transient increase of cholic acid in the first postvagotomy week, but a decrease after the sixth week. They also found that chenodeoxycholic acid increased after the sixth week though it decreased in the first week[49]. We have found, however, an increase in both chenodexycholic and deoxycholic acid and a decrease in the total bile acids after truncal vogotomy. Changes of bile components which we have found in the TV-group, such as a decrease of total bile acids, particulary a decrease of cholic acid, an increase of cholesterol, and decreases in the ratios of TBA/C, PL/C, and trihydroxycholanoic acid to dihydroxycholanoic acid appear to be inducing factors for lithogenic bile. On the other hand, all the biliary components and ratios returned to normal after the sixth postvagotomy week in the SV-group, indicating that this transient change is caused by the influence of surgical intervention on the biliary system as well as on the gastrointestinal tract.

It is easy to assume that the major biliary components, bile acids and cholesterol, can maintain normal metabolism if the hepatic and posterior celiac branch of the vagus nerves are preserved in the vagotomy since the present study shows clearly that the difference in changes of the biliary components between the two groups depends upon the difference in the vagotomy procedures. Care should be taken, therefore, to preserve the hepatic and posterior celiac branches of the vagus nerves in performing not only vagotomy for peptic ulcers but also total or proximal gastrectomy for malignant tumors of the esophagus and the stomach in order to minimize or to eliminate the above-mentioned miscellaneous postvagotomy side effects.

## Summary

Various untoward side effects of vagotomy have been reported by many investigators since the introduction of this procedure in the surgical treatment of peptic ulcers. Among them have been interesting reports of a high incidence of cholecystitis or cholelithiasis after vagotomy. We paid attention to this and designed experimental studies to investigate the effect of the vagus nerves on the biliary system in relation to the pathogenesis of lithogenic bile in ten healthy adult mongrel dogs, divided into two groups, one with complete truncal vagotomy (TV) and the other with selective gastric vagotomy (SV).

The TV-group showed that 1) total bile acids and 2) cholic acid decreased significantly while 3) chenodeoxycholic and 4) deoxycholic acid increased and 5) the ratio of trihydroxycholanoic acid to dihydroxycholanoic acid decreased. These changes persisted from the fourth to the twenty-fourth postvagotomy week; 6) cholesterol tended to increase but 7) phospholipids did not show any remarkable change; 8) the ratio of TBA/C tended to decrease progressively after vagotomy, while 9) the ratio of PL/C showed a significant decrease in the twenty-fourth week only.

In the SV-group, transitional changes of the biliary components and the ratios were observed between the fourth and the sixth postvagotomy week. However, they returned to normal after the eighth week, suggesting that these transitory changes were caused by the operative intervention. 10) It is clear that the definite difference in the various parameters between the two groups is produced by the difference in surgical procedures between them, suggesting the possibility that the hepatic and posterior celiac branches play an important role.

In the present study we saw 11) cholesterol gall stones in neither the TV-group nor the SV-group. A possible explanation is that the concentration of cholesterol is much lower in dogs than in human bile. When bile acids, cholesterol, and phospholipids are plotted in an ADMIRAND's triangular coordinate[50], they are always found in the micellar zone. It is interesting, however, 12) to note that more than half of the animals receiving truncal vagotomy had amorphous pigment stones or sand in their gall bladders, suggesting that complete vagal denervation of the biliary system may produce an unstable bile which cannot hold bile pigments in solution either.

These results indicate 13) that truncal vagotomy can make bile lithogenic. It should be emphasized, therefore, that it is important to preserve the hepatic and the posterior celiac branches while performing vagotomy for peptic ulcers as well as total gastrectomy for malignant neoplasms of the esophagus and stomach.



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## 和文抄録

# 胆汁組成よりみた迷走神経切断術式に関する批判

大阪北逓信病院外科

小　牧　勝　彦

1943年 Dragstedt によって消化性潰瘍に対して迷走神経切断術が施行されて以来，その術式によって生ずる種々の合併症が問題視され，現在までに報告されてきた．その中でも我々は迷走神経切断後，胆嚢疾患の発生率が高いという報告に着目し，その原因を追求するとともに迷走神経幹切断術(Truncal Vagotomy, TV-group)選択的胃迷走神経切断術 (Selective Gastric Vagotomy, SV-group) の胆嚢内胆汁組成に及ぼす影響を比較検討した．

雑成犬にて，両術式を施行し，胆嚢内胆汁を採取，これを分析，胆嚢内胆汁成分の変動を24週間にわたって追跡した．その結果，いくつかの新しい知見を得た．すなわち，TV 群は，

1) 総胆汁酸量 (TBA) が減少する．
2) コール酸も有意の減少を示す
3) デオキシコール酸，ケノデオキシコール酸は増加する．
4) 従って Trihydroxycholanoic acid / Dihydroxycholanoic acid 比は減少する．これらの変化は4～6週の早期に出現し，24週間持続した．
5) コレステロール (C) はやゝ増加の傾向にあるが燐脂質 (PL) は著しい変化を示さない．
6) TBA/C 比は徐々に減少し，
7) PL/C 比は24週目にのみ有意の減少を示す．

一方 SV 群においては胆汁中各成分は4～6週に一時変化はしても8週目には元にもどった．4～6週目の変化は手術そのものの影響と考えられる．

以上の変化は，TV 群にみられて，SV 群にはみられないところから肝枝及び腹腔枝が関与している．

TV 群でも，SV 群でも，犬ではコレステロールが極少量のため，コレステロール結石は出来ず，総胆汁酸，コレステロール，燐脂質の三者の関係から Small の三角図表を作製しても，いづれの時期もミセル帯外に移動しなかった．しかしながら TV 群の3分の2にビリルビン結石又は胆砂を生じたことは胆汁中の組成が不安定なものであることを示している．

以上の点から，迷走神経幹切断後は胆汁成分のわづかな変化から，結石形成の可能性が推測される．従って良性疾患，悪性疾患をとわず，手術の際には，肝枝及び腹腔枝は温存すべきである．